REMARKS

The Claims are Not Obvious

The Examiner has AGAIN rejected Claims 49-57 under 35 U.S.C. Section 103(a) as allegedly being unpatentable over Skurkovich et al. (US 5,888,511) in view of Starnes et al. (*J. Immunol.*, 1990, vol. 145, pp. 4185-4191) and further in view of Doherty et al. *J. Immunol.*, 1990, vol. 149, pp. 1666-1670). Applicant disagrees.

A. Skurkovich is non-analogous art.

Skurkovich is directed to the treatment of autoimmune disease, not to sepsis. The Federal Circuit has outlined a basic definition for non-analogous art:

> The determination whether prior art is analogous involves some factual issues concerning whether the reference is within the field of the inventor's endeavor or reasonably pertinent to the particular problem with which the invention was involved.

Finish Engineering Co., Inc. v. Zerpa Industries, Inc., 806 F.2d 1041, 1 USPQ2d 1114, 1116 (Fed. Cir. 1986). Treating autoimmune disease is not "within the field of the inventor's endeavor". The problem Applicant seeks to solve is the morbidity and mortality associated with sepsis. Thus, Skurkovich is not "reasonable pertinent to the particular problem to which the invention was involved". The Examiner is reminded that the determination of whether an inventor would consider a specific reference is based upon the expressed purpose of the reference:

> If a reference disclosure has the same purpose as the claimed invention, the reference relates to the same problem ... If it is directed to a different purpose, the inventor would accordingly have had less motivation or occasion to consider it.

Since Skurkovich has a different purpose, there is no reason for one skilled in the art to consider it. The Examiner has offered no reasons why one seeking to treat sepsis would even look at Skurkovich.

B. The Examiner has provided only conclusory statements

Skurkovich is non-analogous art and there is no rational basis for combining it. The Examiner has offered only the conclusory statement that "the disclosures of Starnes and Doherty would provide one of ordinary skill in the art with the motivation to administer the composition taught by Skurkovich." Why? Back in 1999,[1] when the Starnes publication was cited by Examiner Hamud, he admitted that "Starnes et al do **not** disclose a composition comprising **both** antibodies to TNF-α and IL-6 or a method of treatment with such composition." (Office Action, mailed 07/02/99, p. 3, emphasis added). Similarly, the Examiner noted that Doherty did not administer combinations, but used "**either** anti-IFN- polyclonal antibodies or anti-TNF- polycloncal antibodies . . ." (p. 3-4, emphasis added). In view of these facts, why don't the disclosure of Starnes and Doherty simply motivate one to use the antibodies independently? Certainly, Skurkovich contributes nothing to the question of what would be effective treatment for sepsis. Thus, one skilled in the art looking to solve the sepsis problem sees only single antibody solutions from Starnes and Doherty. The Examiner has no basis for jumping from the single antibody solutions of Starnes and Doherty to a three antibody combination. The Examiner is reminded that the Supreme Court demands a rational basis for combining art, not merely conclusory statements. In other words, a specific showing by the Examiner is required:

> Often, it will be necessary ... to look to interrelated teachings of multiple patents ... in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. See, *In re Kahn*, 441 F.3d 977, 988 (CA Fed. 2006) ("[R]ejections on obviousness grounds **cannot be sustained by mere conclusory statements**; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness").

KSR v. Teleflex, Slip Op No. 04-1350 (April 30, 2007). It is not enough to find a three antibody combination out of the sepsis context and simply state that one skilled in the art trying to solve sepsis would somehow put it in context. Moreover, in 1999, Applicant introduced the Opal et al. to show that there is sepsis literature which teaches away from combinations: "Combination anticytokine therapy may exacerbate systemic infection and worsen [the] outcome in experimental sepsis." (see response filed in October of 1999, Tab A, Abstract, last line). The

[1] Applicant protests the return to prior art that was cited in 1999 and then removed. This is unfair and costly.

Examiner is not free to ignore this contrary literature (which is already in the record).

C. The Examiner has misunderstood the case law

The Examiner cites *In re Keller* and *In re Merck & Co.* for the proposition that one cannot attack references individually when they have been used by the Examiner in a combination. The Examiner has either not read these cases or has misunderstood them. Specifically, *In re Keller* was decided upon an affidavit that discussed only one of three cited references:

> As characterized by appellant, the Cywinski affidavit offered as objective evidence of non-obviousness "concerns itself mainly with the question of whether the Walsh et al. article suggest[sic] the use of ..." ... In the present case, we are not presented with a single prior art reference, but rather two combinations of three references. ... The affidavit does not indicate that Dr. Cywinski ... critically reviewed ... the two combinations of references.

In re Keller, 642 F.2d 413, 425-426, 208 USPQ 871 (CCPA 1981). Similarly, the citation relied upon by the Examiner within *In re Merck & Co.* supports a finding by the Federal Circuit that the presentation of a non-obviousness argument to only one cited reference (out a total of nine) is insufficient to overcome an obviousness rejection:

> We also find untenable appellant's arguments that Petersen teaches away from appellants' invention. ... Thus, Petersen must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole.

In re Merck & Co., 800 F.2d 1091 1097, 231 USPQ 375 (Fed. Cir. 1986). Thus, these cases apply to the situation where only one reference is rebutted and where the applicant remains silent on the other references in the combination. This is not the case here. Applicant has provided an organized argument regarding each of the three references. Applicant has pointed out the deficiencies in Starnes and Doherty. Applicant has noted that these cannot be remedied by a combination with Skurkovich without a basis for the combination. This is consistent with more recent Federal Circuit precedent states that references must be evaluated individually for their specific motivation to one skilled in the art, without hindsight, before the combination can be made. *In re Rouffet*, 149 F.3d 1350, 476 USPQ2d 1453, 1458 (Fed. Cir. 1998). In any further office action, the Examiner must respond to both Applicant's analysis of *Keller* and *Merck*, as

well as Applicant's citation to *Rouffet*.

D. The Examiner's position is arbitrary

In the previous response, Applicant pointed to the data in Table 5: "The Applicant achieved an unexpected result, however, and overcame the morbidity by administering the combination of anti-TNF antibodies, anti-IFN-γ antibodies and anti-IL-6 antibodies, as shown in Table 5." Moreover, Applicant asked the Examiner "to take note of the *degree of improved results* obtained with the combination (e.g. 100% survival in Table 5 in a "rescue from lethality" experiment)." Applicant pointed to the *Adams* case in support.

In response, the Examiner fails to address the *Adams* case. Moreover, the Examiner fails to address the question of "degree." Instead, the Examiner questions the data and speculates – without a basis – about possible results of other experiments.

With respect to questioning the data, the Examiner states that "One of skill in the art would not know whether the results presented in Table 5 are truly unexpected, or are merely differences due to the timing of antibody administration after LPS challenge." In response, please see the attached declaration of Dr. Stafford (at paragraph 5) who points out that that with respect to the data in Table 5: "These differences are NOT due to the timing of administration, since the timing was the same (i.e. 5 minutes post-challenge)."

With respect to speculating about other experiments, the Examiner asks whether "administration of anti-IFN-γ, or combined anti-IFN-γ and anti-TNF-α antibodies at 5 minutes post-challenge offer the same degree of protection as the combination of all three antibodies at 5 minutes post challenge." In response, please see the attached declaration of Dr. Stafford (at paragraph 6) who discusses the percent survival numbers in Table 5 and concludes: "there is nothing in Table 5 to suggest that single antibodies or two antibody combinations could achieve 100% survival." In making this conclusion, Dr. Stafford emphasizes the "degree" of success and failure (something the Examiner appears to overlook). It is not a question of getting <u>some</u> benefit with the claimed three antibody combination; it is a question of getting such excellent results (100% survival) in the face of poor results with other single antibody and double antibody preparations: "the 100% result is quite unexpected in view of the rather poor results obtained with single antibody and two antibody combinations." (see Declaration, paragraph 6).

The Examiner is not free to ignore this evidence, which has now been clarified by one

skilled in the art. The Examiner has been provided unexpected results within the confines of Table 5. While there are other results in the specification, Applicant believes the data in Table 5 is quite sufficient to establish the point. Failure to accept this data as unexpected is arbitrary and improper, in view of the record.

E. Certain Claims have been amended

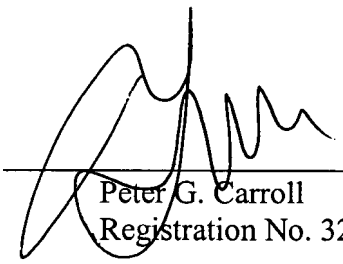
Without waiving any of the above points, Applicant has amended the composition claims (Claims 51, 54 and 57) to specify avian antibodies. The amendments are made without acquiescing to the Examiner, but to further the prosecution and better define one embodiment. Applicant hereby explicitly reserves the right to prosecute the original (or similar) claims in the future.

CONCLUSION

The Applicant believes that the arguments set forth above traverse the Examiner's rejections and, therefore, request that all grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe a telephone interview would aid in the prosecution of this application, the Applicant encourages the Examiner to call the undersigned at 617.984.0616.

Respectfully submitted,

Dated: October 17, 2007



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